Pharmaceutical Approval Update

Marvin M. Goldenberg, PhD, RPh, MS

Belinostat (Beleodaq)

Manufacturer: Spectrum Pharmaceuticals, Inc., Irvine, California

Date of Approval: July 3, 2014

Indication: Belinostat is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication received accelerated approval based on tumor response rate and duration of response.

Drug Class: Belinostat is a novel hydroxamic acid-type histone deacetylase (HDAC) inhibitor with antineoplastic activity. Chemically, it is (2E)-*N*-hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide with a molecular mass of 318.35.

Uniqueness of Drug: Belinostat targets HDAC enzymes, thereby inhibiting tumor cell proliferation, inducing apoptosis, promoting cellular differentiation, and inhibiting angiogenesis. This agent may sensitize drug-resistant tumor cells to other antineoplastic agents, possibly through a mechanism involving the down-regulation of thymidylate synthase.

Warnings and Precautions:

Blood disorders. Belinostat can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and/or anemia; monitor blood counts weekly during treatment and modify dosage as necessary.

Infections. Serious and sometimes fatal infections, including pneumonia and sepsis, have occurred with belinostat. Do not administer belinostat to patients with an active infection. Patients with a history of extensive or intensive chemotherapy may be at higher risk of life-threatening infections.

Liver problems. Belinostat can cause fatal hepatotoxicity and liver function test abnormalities. Monitor liver function tests before treatment and before the start of each cycle. Interrupt or adjust dosage until recovery, or permanently discontinue belinostat based on the severity of the hepatic toxicity.

Tumor lysis syndrome. Tumor lysis syndrome occurred in patients treated with belinostat in the clinical trial of patients with relapsed or refractory PTCL. Monitor patients with advanced disease and/or high tumor burden and take appropriate precautions.

Gastrointestinal effects. Nausea, vomiting, and diarrhea occur with belinostat and may require the use of antiemetic and antidiarrheal medications.

Fetal harm. Belinostat can cause fetal harm when administered to a pregnant woman. Women who can bear children should be advised to avoid pregnancy while receiving belinostat. If belinostat is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of potential hazard to the fetus.

Dosage and Administration: An intravenous (IV) dose of 1,000 mg/m^2 a day is infused over 30 minutes on days 1 to 5 of a 21-day cycle. Cycles can be repeated every 21 days until disease progression or unacceptable toxicity.

Commentary: PTCL comprises a group of rare and aggressive non-Hodgkin's lymphomas (NHLs) that develop from mature T cells and accounts for approximately 10% to 15% of all NHL cases in the U.S. These patients generally have a poor prognosis with a low response rate (25% to 27%) to available treatment options, and commonly experience repeated treatment failures until drug resistance or death. Therefore, there has been an important unmet medical need for additional treatment options that are specifically effective for this disease.

HDAC inhibitors such as belinostat catalyze the removal of acetyl groups from the lysine residues of histones and some nonhistone proteins. *In vitro,* belinostat causes the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Belinostat shows preferential cytotoxicity toward tumor cells compared with normal cells. Belinostat inhibits the enzymatic activity of histone deacetylases at nanomolar concentrations (less than 250 nM).

Belinostat works by stopping enzymes that contribute to T cells becoming cancerous. It is intended for patients whose disease returned after treatment (relapsed) or did not respond to previous treatment (refractory).

The Food and Drug Administration (FDA) accelerated approval program allows for approval of a drug based on surrogate or intermediate endpoints reasonably likely to predict clinical benefit for patients who have serious conditions with unmet medical needs. Drugs receiving accelerated approval are subject to confirmatory trials verifying clinical benefit. Belinostat also received the FDA's orphan product designation because it is intended to treat a rare disease or condition.

Sources: www.beleodaq.com, http://online.wsj.com

C1-inhibitor (C1-esterase inhibitor) (Ruconest)

Manufacturer: Pharming Group N.V., Leiden, the Netherlands. Distributed and marketed by Santarus, Inc., a wholly owned subsidiary of Salix Pharmaceuticals, Inc., Raleigh, North Carolina.

Date of Approval: July 18, 2014

Indication: Ruconest is indicated for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE) due to C1-esterase deficiency.

Biological Class: Ruconest is a recombinant C1-esterase inhibitor. Ruconest contains conestat alfa as the active substance. Conestat alfa is a recombinant form of human C1 inhibitor (rhC1INH) and is produced using recombinant DNA technology from the milk of rabbits.

Uniqueness of Biological Agent: Ruconest is the first recombinant human C1-esterase inhibitor (rhC1INH) approved for use in patients with HAE; rhC1INH and plasma-derived C1INH have an identical amino acid sequence.

The *in vitro* inhibitory potency of rhC1INH toward target enzymes is comparable to that of plasma-derived C1INH.

A member of P&T's *editorial board, the author is President of Pharmaceutical and Scientific Services at Marvin M. Goldenberg, LLC, in Westfield, New Jersey. His email address is marvinmgoldenberg@verizon.net.*

Warnings and Precautions:

Hypersensitivity. Patients should not use Ruconest if they are or think they may be allergic to rabbits or if they are allergic to conestat alfa or any of the other ingredients of the product. Patients should only use Ruconest if they have a negative test for rabbit allergy. This test should be repeated every year or after every 10 treatments with Ruconest, whichever occurs first. Patients who experience allergic reactions (e.g., hives, rash, itching, dizziness, wheezing, difficulty breathing, or swelling of the tongue) following the administration of Ruconest should seek emergency medical assistance.

Children and adolescents. Ruconest is not indicated for use in patients younger than 18 years old.

Concomitant medication use. Patients should inform the physician if they are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Blood clots. Patients who are receiving acute treatment for blood clots should not be treated with Ruconest at the same time.

Pregnancy and breast-feeding. Use of Ruconest is not recommended during pregnancy or breast-feeding. Women who are planning to become pregnant should talk with their doctors before starting to use Ruconest.

Driving and using machines. Patients should not drive or use machinery if they feel dizzy or experience a headache after using Ruconest.

Dosage and Administration: Treatment with Ruconest should be started under the supervision of a physician with experience in diagnosing and treating HAE. The medicine should only be given by a health care professional. Patients who have not received Ruconest before should be tested to see if they have antibodies against rabbit dander in their blood; they should be given Ruconest only if their tests are negative.

Ruconest is given by slow injection into a vein. The dose depends on the patient's body weight. One injection is usually enough to treat an attack, but a second injection may be given if the patient does not improve enough after the first one. A patient should not be given more than two injections in a 24-hour period.

For persons weighing less than 84 kg, 50 IU/kg should be infused over five minutes; the dose should not exceed 4,200 IU. For persons weighing 84 kg or more, 4,200 IU should be infused over five minutes.

If the attack symptoms persist, a second dose may be administered at the recommended dose level (not to exceed 4,200 IU/dose). Most patients have been treated successfully with the 50-IU/kg dose; only about 10% of patients have needed a second dose.

Commentary: Ruconest is the first recombinant human C1-esterase inhibitor developed and approved for the treatment of acute angioedema attacks in HAE patients. Use of a well-controlled transgenic platform for the production of Ruconest ensures that product supply is virtually unlimited and avoids the risk of transmission of human blood-borne infections.

Sources: www.ruconest.com, www.rxlist.com, www.marketwatch.com

Tedizolid Phosphate (Sivextro)

Manufacturer: Cubist Pharmaceuticals, Inc., Jersey City, New Jersey

Date of Approval: June 20, 2014

Indication: Sivextro treats adult acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), which has been categorized by the Centers for Disease Control and Prevention (CDC) as a serious public health threat.

Drug Class: Tedizolid phosphate, the prodrug of tedizolid, is an antibacterial agent. Tedizolid phosphate's International Union of Pure and Applied Chemistry name is (5R)-3-{3-fluoro-4-[6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl]phenyl}-5-(hydroxymethyl)-1,3-oxazolidin-2-one. Tedizolid phosphate has a molecular weight of 450.318.

Uniqueness of Drug: Tedizolid is a novel oxazolidinone antibacterial that binds to the 50S subunit of the bacterial ribosome, resulting in inhibition of protein synthesis. Tedizolid inhibits bacterial protein synthesis through a mechanism of action different from that of other nonoxazolidinone class 13 antibacterial drugs; therefore, cross-resistance between tedizolid phosphate and other classes of antibacterial drugs is unlikely.

Warnings and Precautions:

Patients with Neutropenia. The safety and efficacy of tedizolid phosphate in patients with neutropenia (neutrophil counts less than 1,000 cells/mm^3) have not been adequately evaluated. In an animal model of infection, the antibacterial activity of tedizolid phosphate was reduced in the absence of granulocytes. Alternative therapies should be considered when treating patients with neutropenia.

Clostridium difficile–*associated diarrhea (CDAD).* Ranging from mild diarrhea to fatal colitis, CDAD has been reported with nearly all systemic antibacterial agents, including tedizolid phosphate. Evaluate all patients who present with diarrhea following tedizolid phosphate use.

Development of drug-resistant bacteria. Prescribing tedizolid phosphate in the absence of a proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Dosage and Administration: Tedizolid phosphate will be available as 200-mg tablets in 30-count bottles and six-tablet blister packs, and in 200-mg single-dose vials as a sterile, lyophilized powder for injection. Each 200-mg vial must be reconstituted with sterile water for injection and subsequently diluted only with 0.9% sodium chloride injection, USP, as an IV infusion only.

Commentary: Tedizolid phosphate addresses ABSSSIs caused by susceptible gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). Tedizolid phosphate 200 mg administered once daily for six days was statistically noninferior to 600 mg of linezolid taken twice a day for 10 days. In these studies, the adverse event rates were similar for patients treated with tedizolid phosphate and linezolid. Linezolid, an oxazolidinone, is the only oral drug approved for complicated skin and skin structure infections caused by MRSA.

Tedizolid phosphate allows physicians the flexibility to transition patients from IV to oral treatment as needed. The oral option provides an opportunity for outpatient care, which could

continued on page 626

Pharmaceutical Approval Update

continued from page 620

lower the requirement for costly hospitalization.

Sivextro is one of three new antibacterial drugs approved by the FDA in the past few months to treat ABSSSIs. The agency approved dalbavancin (Dalvance, Durata Therapeutics) in May and oritavancin for injection (Orbactiv, The Medicines Company) in August; both treat patients with ABSSSIs caused by *Staphylococcus aureus* and various Streptococcus species.

Sivextro benefits from the Generating Antibiotic Incentives Now (GAIN) Act passed by Congress in 2012 to encourage antibiotic development. The GAIN Act offers antibiotic drug-makers faster FDA review and five years of additional patent exclusivity to sell their product without generic competition. Cubist acquired Sivextro in 2013 with its $707 million purchase of Trius Therapeutics; it also bought Optimer Pharmaceuticals to acquire access to another product, Dificid (fidaxomicin), a macrolide antibacterial for the treatment of CDAD.

Sources: www.sivextro.com, www.thepharmaletter.com, www.pewtrusts.org ■